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Title of Invention _____

Inventors (please provide full names): _____

_____

Earliest Priority Date: _____

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FILE COVERS 1967 - 14 Oct 1999  VOL 131 ISS 16
FILE LAST UPDATED: 13 Oct 1999  (19991013/ED)
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L8        40332 SEA FILE=CAPLUS ABB=ON  COMPLEMENT
L11         762 SEA FILE=CAPLUS ABB=ON  CTLA(W)4##
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L15           1 SEA FILE=CAPLUS ABB=ON  L14 AND (L4 OR L11)


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L19           6 SEA FILE=CAPLUS ABB=ON  L18 AND (L4 OR L11)


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L31         202 SEA FILE=CAPLUS ABB=ON  L29(L)(INHIBIT? OR DECREAS? OR REDUC?
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L86 13 L15 OR L19 OR L32 OR L34

=> fil medl; d que l53; d que l54; s l53 or l54
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L41 29912 SEA FILE=MEDLINE ABB=ON IMMUNOGLOBULINS/CT
L49 24546 SEA FILE=MEDLINE ABB=ON IMMUNOSUPPRESSIVE AGENTS/CT
L52 852 SEA FILE=MEDLINE ABB=ON CTLA4? OR CTLA(W)4##
L53 1 SEA FILE=MEDLINE ABB=ON L52 AND L41 AND L49

L38 35766 SEA FILE=MEDLINE ABB=ON COMPLEMENT+NT/CT
L39 64139 SEA FILE=MEDLINE ABB=ON MACROPHAGES+NT/CT
L41 29912 SEA FILE=MEDLINE ABB=ON IMMUNOGLOBULINS/CT
L42 3158 SEA FILE=MEDLINE ABB=ON L41(L)BI/CT - Subheading - Biosynthesis
L52 852 SEA FILE=MEDLINE ABB=ON CTLA4? OR CTLA(W)4##
L54 13 SEA FILE=MEDLINE ABB=ON L52 AND (L38 OR L42 OR L39)

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L55 896 SEA FILE=BIOSIS ABB=ON CTLA4? OR CTLA(W)4##
L57 33327 SEA FILE=BIOSIS ABB=ON (GAMMA OR (TYPE(W)(2 OR II)))(A)INTERFERON#

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L67          173 SEA FILE=BIOSIS ABB=ON  L55(8A)(INHIBIT? OR MODULAT? OR
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L88           15 L60 OR L65 OR L72 OR L74

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L89          37 DUP REM L87 L88 L86 L82 (6 DUPLICATES REMOVED)

=> d ibib ab 1-37; fil hom

L89  ANSWER 1 OF 37  CAPLUS  COPYRIGHT 1999 ACS
ACCESSION NUMBER:        1999:622174  CAPLUS
TITLE:                   Methods and compounds for prevention of graft
                         rejection
INVENTOR(S):             Strom, Terry; Libermann, Towia
PATENT ASSIGNEE(S):      Beth Israel Hospital Association, USA
SOURCE:                  U.S., 37 pp., Cont.-in-part of U.S. Ser. No. 24,569,
                         abandoned.
                         CODEN: USXXAM
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     US 5958403         A    19990928      US 1994-273402   19940711
PRIORITY APPLN. INFO.:                     US 1992-843731   19920228
                                           US 1993-24569    19930301

AB   Disclosed is a method of localized immunosuppression which may be used for
     preventing graft rejection or for preventing tissue destruction due to
     autoimmune disease. Also disclosed is a protein suppressor factor
     (IL-2.15) that is secreted by cloned anergic T-cells, blocks interleukin 2
     (IL-2) stimulated T-cell proliferation, has an apparent mol. wt. of
     between 10 and 30 kDa, can be inactivated by heating to 65.degree. C. for
     15 min, blocks interleukin 4 (IL-4) stimulated T-cell proliferation in
     vitro, is non-cytotoxic to T-cells, and does not inhibit the prodn. of
     IL-2 by T-cells in vitro. Graft rejection is prevented by inducing a
     state of local immunosuppression at the transplant site with expression of
     recombinant proteins by the allograft. According to the claims, the
     method comprises: (a) introducing in an islet cell, ex vivo, a nucleic
     acid sequence encoding CTLA4-Ig operably linked to a promoter,
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wherein the **CTLA4**-Ig is expressed by the islet cell; and (b) transplanting the islet cell into the patient, wherein **CTLA4**-Ig is expressed at a level sufficient to inhibit the rejection of the transplanted cell.

L89 ANSWER 2 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 1999:379673 BIOSIS
DOCUMENT NUMBER: PREV199900379673
TITLE: **CTLA-4** blockade enhances the immune response induced by mycobacterial infection but does not lead to increased protection.
AUTHOR(S): Kirman, Joanna; McCoy, Kathy; Hook, Sarah; Prout, Melanie; Delahunt, Brett; Orme, Ian; Frank, Anthony; Le Gros, Graham (1)
CORPORATE SOURCE: (1) Malaghan Institute of Medical Research, Wellington South New Zealand
SOURCE: Infection and Immunity, (Aug., 1999) Vol. 67, No. 8, pp. 3786-3792.
ISSN: 0019-9567.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The murine immune response to a pulmonary mycobacterial infection is slow to develop, allowing bacterial numbers to increase in the lung for several weeks after infection. We sought to enhance the protective immune response induced during Mycobacterium bovis BCG infection by administering an antibody that blocks the interaction of **CTLA-4** with its ligands, CD80 and CD86. We found that injection of anti-**CTLA -4** monoclonal antibody (MAb) greatly enhanced and accelerated the immune response, as measured by increased cellularity of the draining mediastinal lymph nodes, and **enhanced** antigen-inducible proliferation and **gamma interferon** production by mediastinal lymphocytes in vitro. However, despite the apparently enhanced immune response in the mediastinal lymph node following treatment with anti-**CTLA-4** MAb, there was no improvement in clearance of mycobacteria in the lungs, liver, or spleen. Examination of the primary site of infection, the lung, revealed that **CTLA-4** blockade had no effecton the number or function of lymphocytes infiltrating the infected lung tissue. Taken together, these data suggest that in vivo **CTLA-4** blockade enhances mycobacterial-infection-induced lymphocyte expansion and effector cell cytokine production in the draining lymph node but does not alter the number or function of lymphocytes at the primary site of infection and therefore does not lead to enhanced clearance of the infection.

L89 ANSWER 3 OF 37 MEDLINE
ACCESSION NUMBER: 1999280639 MEDLINE
DOCUMENT NUMBER: 99280639
TITLE: Expression of costimulatory molecules on alveolar macrophages in hypersensitivity pneumonitis.
AUTHOR: Israel-Assayag E; Dakhama A; Lavigne S; Laviolette M; Cormier Y
CORPORATE SOURCE: Unite de Recherche, Centre de Pneumologie, Hopital Laval, Ste. Foy; and Institut de Cardiologie et de Pneumologie, Universite Laval, Ste. Foy, Quebec, Canada.
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (1999 Jun) 159 (6) 1830-4.
Journal code: BZS. ISSN: 1073-449X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990901
AB To verify whether alveolar macrophages (AM) of patients with hypersensitivity pneumonitis (HP) increase their antigen-presenting capacity by upregulating the expression of B7 costimulatory molecules (CD80, CD86), and whether a viral infection enhances this expression whereas cigarette smoking abrogates it, we performed bronchoalveolar lavage (BAL) on 18 patients with HP; 10 asymptomatic, virus-exposed subjects (AS); 18 nonsmokers; and 12 smokers. Influenza virus infection of AM from nonsmokers and smokers was induced in vitro. Expression of CD80 and CD86 on AM, and of CD28 and **CTLA4** on T cells, was evaluated. The percentage of CD80(+) AM was greater in HP patients (34.6 +/- 7.7) and in AS (23.9 +/- 7.6) than in nonsmokers (6.7 +/- 1.6) or smokers (2.5 +/- 0.3). An increase in CD86(+) cells (62.3 +/- 5.9) was found in HP patients as compared with nonsmokers (24.2 +/- 3.8) and smokers (4.5 +/- 1.0). CD28 and **CTLA4** molecules were highly expressed on all T cells. In vitro virus infection upregulated CD80 and CD86 expression in AM of normal nonsmoking subjects but not on those of smokers. These results suggest that: (1) an upregulation of B7 molecule expression is involved in the lymphocytic alveolitis of HP; (2) a viral infection could enhance HP by increasing B7 expression; and (3) the protective effect of cigarette smoking in HP may be due to the low level of expression of costimulatory molecules on AM from smokers, and to their resistance to further upregulation.

L89 ANSWER 4 OF 37 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1999:101512 CAPLUS
DOCUMENT NUMBER: 130:266268
TITLE: Blocking OX-40/OX-40 ligand interaction in vitro and in vivo leads to decreased T cell function and amelioration of experimental allergic encephalomyelitis
AUTHOR(S): Weinberg, Andrew D.; Wegmann, Keith W.; Funatake, Castle; Whitham, Ruth H.
CORPORATE SOURCE: Robert W. Franz Cancer Research Center, Providence Portland Medical Center, Earle A. Chiles Research Institute, Portland, OR, 97213, USA
SOURCE: J. Immunol. (1999), 162(3), 1818-1826
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The OX-40R is a member of the TNF receptor family and is expressed primarily on activated CD4+ T cells. When the OX-40R is engaged by the OX-40 ligand (OX-40L), a potent costimulatory signal occurs. The authors have identified a population of CD11b+ cells, isolated from the central nervous system (CNS) of mice with actively induced exptl. allergic encephalomyelitis (EAE), that expresses OX-40L. Moreover, the expression of OX-40L was assocd. with paralytic episodes of EAE and was reduced or absent at disease recovery. These CD11b+ cells also coexpressed B7 and MHC class II. Therefore, to address the relative contributions of OX-40R/OX-40L and CD28/B7 to the costimulation of myelin-specific T cells, blocking studies were performed using sol. OX-40R and/or sol. **CTLA-4**. CD11b+ cells isolated from the CNS of mice with actively induced EAE were able to present Ag to proteolipid protein 139-151-specific T cell lines in vitro. The addn. of sol. OX-40R:Ig to CD11b+ brain microglia/**macrophages inhibited** T cell proliferation by 50-70%. The addn. of **CTLA-4**:Ig inhibited T cell proliferation by 20-30%, and the combination inhibited T cell proliferation by 95%. In vivo administration of sol. OX-40R at the

onset of actively induced or adoptively transferred EAE reduced ongoing signs of disease, and the mice recovered more quickly from acute disease. The data imply that OX-40L, expressed by CNS-derived APC, acts to provide an important costimulatory signal to EAE effector T cells found within the inflammatory lesions. Furthermore, the data suggest that agents designed to inhibit the OX-40L/OX-40R complex may be useful for treating autoimmune disease.

L89 ANSWER 5 OF 37 MEDLINE
ACCESSION NUMBER: 1999173433 MEDLINE
DOCUMENT NUMBER: 99173433
TITLE: Suppressive effects of **CTLA4**-Ig on nasal allergic reactions in presensitized murine model.
AUTHOR: Sato J; Asakura K; Murakami M; Uede T; Kataura A
CORPORATE SOURCE: Department of Otolaryngology, Sapporo Medical University, School of Medicine, Japan.. jsato@sapmed.ac.jp
SOURCE: LIFE SCIENCES, (1999) 64 (9) 785-95.
Journal code: L62. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199906
ENTRY WEEK: 19990601
AB Ag-specific T cell activation requires the engagement of T cell receptor (TCR) with antigen in the context of MHC, and the engagement of appropriate costimulatory molecules. It is well established that B7/CD28-**CTLA4** costimulatory pathway plays an important role in the induction of T helper (Th) cells in T-cell dependent immune reactions. In this study, we evaluated the effects of blocking the costimulatory pathway by systemic administration of **CTLA4**-Ig during repeated nasal antigen challenges in systemically presensitized mouse. The antigen-induced early phase nasal symptoms, nasal hyperresponsiveness to histamine and nasal eosinophilia were significantly suppressed by **CTLA4**-Ig treatment. Elevation of serum level of antigen-specific IgE, but not IgG1 or IgG2a was inhibited by the treatment. In relation to cytokine levels in the tissue extracts of the nasal mucosa, an up-regulation of IL-4 was significantly inhibited, however, the levels of IL-5 and IFN-gamma were not affected by the treatment. These results suggest that B7/CD28-**CTLA4** costimulatory pathway plays an important role in on-going Th2-related allergic reactions in the nose.

L89 ANSWER 6 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 1999:249097 BIOSIS
DOCUMENT NUMBER: PREV199900249097
TITLE: A role for CD45RBlow CD38+ T cells and costimulatory pathways of T-cell activation in protection of non-obese diabetic (NOD) mice from diabetes.
AUTHOR(S): Martins, T. C. (1); Aguas, A. P.
CORPORATE SOURCE: (1) Institute for Molecular and Cell Biology, R. Campo Alegre, 823, 4150, Porto Portugal
SOURCE: Immunology, (April, 1999) Vol. 96, No. 4, pp. 600-605.
ISSN: 0019-2805.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Non-obese diabetic (NOD) mice spontaneously develop autoimmune insulin-dependent diabetes mellitus (IDDM). Infection of the animals with mycobacteria, or immunization with mycobacteria-containing adjuvant, results in permanent protection of NOD mice from diabetes and we have recently reported that the phenomenon is associated with **increased**

numbers of **interferon-gamma**-producing T cells, possessing **increased** cytotoxic activity, and also with augmented numbers of activated immunoglobulin M-positive (IgM+) B cells. Here, we have investigated whether protection of NOD mice from IDDM was associated with changes on costimulatory pathways of T and B cells, namely CD28/ **CTLA-4**-B7 and CD40-CD40 ligand (CD40L) and we also further characterized protective T helper (Th) cells with regards to the expression of the differentiation markers CD45RB and CD38. We report that Th cells involved in diabetes vaccination of NOD mice by mycobacterial infection seem to belong to CD45RBlo CD38+ phenotype. The protective effect of Mycobacterium avium infection is also associated with increased CD40L and **CTLA-4**-expressing Th cells and with the generation of a CD40- IgG+ B cells. Our data are consistent with induction by mycobacterial infection of regulatory CD45RBlo CD38+ Th cells with the ability to trigger deletion or anergy of peripheral self-reactive lymphocytes, with shutting down of IgG+ B-cell response. They also implicate a role for IgG+ B cells in the autoimmune aggression of the endocrine pancreas of NOD mice.

L89 ANSWER 7 OF 37 MEDLINE
ACCESSION NUMBER: 1999309109 MEDLINE
DOCUMENT NUMBER: 99309109
TITLE: Phenotypic analysis of lymphocytes and monocytes/macrophages in peripheral blood and bronchoalveolar lavage fluid from patients with pulmonary sarcoidosis.
AUTHOR: Wahlstrom J; Berlin M; Skold C M; Wigzell H; Eklund A; Grunewald J
CORPORATE SOURCE: Microbiology and Tumour Biology Centre, Karolinska Institutet, S-171 77 Stockholm, Sweden.
SOURCE: THORAX, (1999 Apr) 54 (4) 339-46.
Journal code: VQW. ISSN: 0040-6376.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990902
AB BACKGROUND: The granulomatous inflammation in sarcoidosis is driven by the interplay between T cells and macrophages. To gain a better understanding of this process the expression by these cells of cell surface activation markers, co-stimulatory molecules, and adhesion molecules was analysed. METHODS: CD4+ and CD8+ T lymphocytes from peripheral blood (PBL) or bronchoalveolar lavage (BAL) fluid, as well as paired peripheral blood monocytes and alveolar macrophages from 27 patients with sarcoidosis were analysed by flow cytometry. RESULTS: CD26, CD54, CD69, CD95, and gp240 were all overexpressed in T cells from BAL fluid compared with those from PBL in both the CD4+ and CD8+ subsets, while CD57 was overexpressed only in BAL CD4+ cells. In contrast, CD28 tended to be underexpressed in the BAL T cells. Monocyte/macrophage markers included CD11a, CD11b, CD11c, CD14, CD16, CD54, CD71, CD80 and CD86 and HLA class II. CD11a expression in alveolar macrophages (and peripheral blood monocytes) was increased in patients with active disease and correlated positively with the percentage of BAL lymphocytes. Expression of CD80 in macrophages correlated with the BAL CD4/CD8 ratio. CONCLUSIONS: Our data indicate substantial activation of both CD4+ and CD8+ lung T cells in sarcoidosis. There were also increased numbers of BAL lymphocytes whose phenotypic characteristics have earlier been associated with clonally expanded, replicatively senescent cells of the Th1 type.

L89 ANSWER 8 OF 37 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:221555 CAPLUS
DOCUMENT NUMBER: 131:72603
TITLE: Blockade of CD28/**CTLA4**-B7 pathway prevented autoantibody-related diseases but not lung disease in MRL/lpr mice
AUTHOR(S): Takiguchi, Mitsuyoshi; Murakami, Masaaki; Nakagawa, Izumi; Yamada, Akira; Chikuma, Shunsuke; Kawaguchi, Yoshinori; Hashimoto, Akira; Uede, Toshimitsu
CORPORATE SOURCE: Section of Immunopathogenesis, Institute of Immunological Science, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, 060815, Japan
SOURCE: Lab. Invest. (1999), 79(3), 317-326
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors studied the role of CD28/**CTLA4** costimulatory T-cell activation pathway on the pathogenesis of MRL/lpr mice. Administration of **CTLA4IgG** from day 0 inhibited autoantibody prodn. such as anti-double-stranded DNA antibody and rheumatoid factor. In addn., end-organ diseases in kidney, salivary gland, and liver were improved. Improvement of pathol. findings coincided with an improvement in survival. At 350 days of age, 90% of mice treated with **CTLA4IgG** from day 0 were still alive, compared with none of mice treated with hIgG. As expected, activation of conventional T cells was inhibited after **CTLA4IgG** treatment. However, lung disease that was characterized by perivascular accumulation and interstitial infiltration of lymphocytes and **macrophages** was not **inhibited**. Even after **CTLA4IgG** treatment from day 0, pathol. findings of lung disease were not improved. Addnl., the expression of activation markers such as B7-1, B7-2, CD71, ICAM1, and LFA1 on Mac1+ fraction in both spleen and lung and the concn. of TNF.alpha. in bronchoalveolar lavage fluid were not suppressed. Thus, lung disease was independent of the CD28/**CTLA4** -B7 pathway. This study emphasizes the differential dependence of the CD28/**CTLA4**-B7 pathway in development of diseases in MRL/lpr mice.

L89 ANSWER 9 OF 37 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:551196 CAPLUS
DOCUMENT NUMBER: 129:259307
TITLE: **CTLA-4** blockade synergizes with tumor-derived granulocyte-macrophage colony-stimulating factor for treatment of an experimental mammary carcinoma
AUTHOR(S): Hurwitz, Arthur A.; Yu, Tina F.-Y.; Leach, Dana R.; Allison, James P.
CORPORATE SOURCE: Howard Hughes Medical Institute, Cancer Research Laboratory, University of California at Berkeley, Berkeley, CA, 94720, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(17), 10067-10071
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Generation of a T cell-mediated antitumor response depends on T cell receptor engagement by major histocompatibility complex/antigen as well as CD28 ligation by B7. **CTLA-4** is a second B7 receptor expressed by T cells upon activation that, unlike CD28, appears to deliver an inhibitory signal to T cells. Recently, the authors and others

demonstrated that administration of an anti-**CTLA-4** antibody was sufficient to promote regression of several murine tumors. However, certain tumors, such as the SM1 mammary carcinoma, remain refractory to this type of immunotherapy. Here, the authors report that the combination of both **CTLA-4** blockade and a vaccine consisting of granulocyte-macrophage colony-stimulating factor-expressing SM1 cells resulted in regression of parental SM1 tumors, despite the ineffectiveness of either treatment alone. This synergistic therapy resulted in long-lasting immunity to SM1 and depended on both CD4+ and CD8+ T cells. Interestingly, synergy was not obsd. between **CTLA-4** and a B7-expressing SM1 vaccine. Given that granulocyte-macrophage colony-stimulating factor promotes differentiation and activation of dendritic cells as well as enhances cross-priming of T cells to tumor-derived antigens and that SM1 is MHC class II-neg., the authors' findings suggest that **CTLA-4** blockade acts at the level of a host-derived antigen-presenting cell. In addn., these results also support the idea that the most effective and synergistic vaccine strategy targets treatments that enhance T cell priming at the level of host-derived antigen-presenting cells.

L89 ANSWER 10 OF 37 MEDLINE
ACCESSION NUMBER: 1999023371 MEDLINE
DOCUMENT NUMBER: 99023371
TITLE: Regulation of T helper cell differentiation in vivo by soluble and membrane proteins provided by antigen-presenting cells.
AUTHOR: De Becker G; Moulin V; Tielemans F; De Mattia F; Urbain J; Leo O; Moser M
CORPORATE SOURCE: Departement de Biologie Moleculaire, Universite Libre de Bruxelles, Rhode-Saint-Gen`ese, Belgium.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Oct) 28 (10) 3161-71. Journal code: EN5. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199902
ENTRY WEEK: 19990204
AB The aim of this study was to test whether the nature of the antigen-presenting cell (APC) can influence the Th1/Th2 balance in vivo. Our data show that dendritic cells (DC), pulsed extracorporeally with antigen, induced the development of cells secreting IL-2, IFN-gamma and IL-4 upon antigen rechallenge in vitro. Priming with peritoneal macrophages sensitized cells that produced IL-4 but not IFN-gamma. To identify the factors involved in T helper development, mice were primed with APC with or without treatment with neutralizing antibodies to costimulatory molecules or cytokines. Our results indicate that priming with DC or macrophages is strictly dependent on the CD28-**CTLA4** /B7 interaction. Of note, CD86 provides the initial signal to induce naive T cells to become IL-4 producers, whereas CD80 is a more neutral differentiation signal. IL-12, released by the DC, appears as a potent and obligatory inducer of differentiation for IFN-gamma-producing cells. IL-6, although produced by both APC populations, is necessary to direct activation of the Th2-type response by macrophages but not by DC.

L89 ANSWER 11 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 3
ACCESSION NUMBER: 1999:58724 BIOSIS
DOCUMENT NUMBER: PREV199900058724
TITLE: Unresponsive CD4+ T lymphocytes from Leishmania chagasi-infected mice increase cytokine production and mediate parasite killing after blockade of B7-1/

CTLA-4 molecular pathway.
AUTHOR(S): Gomes, Nitza A.; Barreto-De-Souza, Victor; Wilson, Mary E.; Dosreis, George A. (1)
CORPORATE SOURCE: (1) Inst. Biofisica Carlos Chagas Filho, Univ. Federal do Rio de Janeiro, Centro Ciencias Saude, Bloco G, Ilha do Fundao, Rio de Janeiro, RJ 21944-970 Brazil
SOURCE: Journal of Infectious Diseases, (Dec., 1998) Vol. 178, No. 6, pp. 1847-1851.
ISSN: 0022-1899.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Infection of BALB/c mice with Leishmania chagasi results in progressive increase of parasite burden in spleen, in spite of extensive T cell activation in situ. Explanted splenic CD4+ T cells showed decreased proliferation to anti-CD3, compared with controls, and no response to L. chagasi recombinant antigen Lcr1. Blockade of the negative costimulatory receptor **CTLA-4** restored responses to and-CD3 and induced vigorous responses to Lcr1. Blockade of B7-1, but not B7-2, also enhanced T cell responsiveness. **CTLA-4** blockade completely restored activation-induced interleukin-2 secretion and **increased interferon-gamma** production. The effect, however, was not restricted to Th1 responses, since **CTLA-4** blockade also enhanced antigen-induced interleukin-4 secretion. **CTLA-4** blockade induced almost complete elimination of parasite burden in splenocyte cultures activated with anti-CD3 or Lcr1. These results indicate that **CTLA-4** engagement by B7-1 plays an important role in maintaining unresponsiveness in CD4+ T cells in this model of chronic visceral leishmaniasis.

L89 ANSWER 12 OF 37 MEDLINE
ACCESSION NUMBER: 1999066324 MEDLINE
DOCUMENT NUMBER: 99066324
TITLE: Flow cytometric analyses of the specific activation of peripheral blood mononuclear cells from healthy donors after in vitro stimulation with a fermented mistletoe extract and mistletoe lectins.
AUTHOR: Stein G M; Berg P A
CORPORATE SOURCE: Krebsforschung Herdecke, Department of Applied Immunology, Communal Hospital, Germany.
SOURCE: EUROPEAN JOURNAL OF CANCER, (1998 Jun) 34 (7) 1105-10.
Journal code: ARV. ISSN: 0959-8049.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199902
ENTRY WEEK: 19990204
AB Immunostimulatory properties of mistletoe extracts derived from Viscum album L. (VAL) are well described, demonstrating activation especially of T, T-helper cells and monocytes/macrophages. In order to characterise in detail the communication between different cell populations, we studied mistletoe-induced expression of co-stimulatory signals and their ligands by flow cytometry. Peripheral blood mononuclear cells (PBMC) from 15 healthy controls were incubated for 7 days with a fermented VAL extract. VAL significantly upregulated the expression of the co-stimulatory molecule B7.1 (CD80) on monocytes/macrophages, but not B7.2 (CD86). No significant changes in the expression of either molecules on B cells could be found, suggesting that only monocytes/macrophages act as antigen presenting cells (APCs) in this in vitro system. Purified mistletoe lectins, components of most VAL extracts were also analysed, but did not induce similar responses of monocytes/macrophages. The receptor for B7

molecules, CD28, but not **CTLA-4** (CD152), was also found to be significantly enhanced on CD4+ cells after VAL simulation. There was no evidence for activation of a B cell response via the CD40/CD40L pathway. Our data support the concept that stimulation by VAL extracts induces a specific T-helper cell reaction with monocytes/macrophages acting as APCs and purified lectins do not exert the same effects.

L89 ANSWER 13 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1998:204706 BIOSIS
DOCUMENT NUMBER: PREV199800204706
TITLE: Blockade of CD28/CTLA4 pathway prevented almost diseases and lymphadenopathy but not lung disease in MRL/lpr mice.
AUTHOR(S): Takiguchi, Mitsuyoshi; Murakami, Masaaki; Nakagawa, Izumi; Yamada, Akira; Chikuma, Shunsuke; Uede, Toshimitsu
CORPORATE SOURCE: Sect. Immunopathogenesis, Inst. Immunol. Sci., Hokkaido Univ., Hokkaido Japan
SOURCE: FASEB Journal, (March 20, 1998) Vol. 12, No. 5, pp. A1093. Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 98, Part II San Francisco, California, USA April 18-22, 1998 Federation of American Societies for Experimental Biology . ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L89 ANSWER 14 OF 37 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:232655 CAPLUS
DOCUMENT NUMBER: 128:326376
TITLE: Immunoliposomes containing antibodies to costimulatory molecules as adjuvants for HIV subunit vaccines
AUTHOR(S): Ozpolat, Bulent; Rao, Xiao-Mei; Powell, Michael F.; Lachman, Lawrence B.
CORPORATE SOURCE: Department of Cell Biology, University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: AIDS Res. Hum. Retroviruses (1998), 14(5), 409-417 CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunoliposomes contg. monoclonal antibodies (MAbs) to the costimulatory mols. CD28 and **CTLA4** and their counter-receptors B7-1 (CD80) and B7-2 (CD86) were evaluated for the ability to increase the immune response to recombinant envelope protein rgp120 of the MN strain of human immunodeficiency virus type 1 (HIV-1) during vaccination. MAbs were attached to rgp120-contg. liposomes via a biotin-avidin-biotin bridge. Mice vaccinated with immunoliposomes were found to have a strong delayed-type hypersensitivity (DTH) response to the weakly immunogenic gp120 that was dependent on the presence of the MAbs. However, this vaccination protocol did not induce humoral immunity. The DTH response was not accompanied by **increased prodn.** of **interferon .gamma.** (IFN-.gamma.) or interleukin 4 (IL-4), implying that the primary cellular interaction was between the immunoliposomes and cells of the reticuloendothelial system and not helper T (Th) cells. This strategy of incorporating antibodies to costimulatory mols. on the surface of antigen-contg. particulates, such as liposomes or microspheres, can be used to increase DTH immune responses to protein or peptide vaccines.

L89 ANSWER 15 OF 37 MEDLINE
ACCESSION NUMBER: 1998143737 MEDLINE

DOCUMENT NUMBER: 98143737
TITLE: Compartmentalization of T cell responses following respiratory infection with Bordetella pertussis: hyporesponsiveness of lung T cells is associated with modulated expression of the co-stimulatory molecule CD28.
AUTHOR: McGuirk P; Mahon B P; Griffin F; Mills K H
CORPORATE SOURCE: Department of Biology, National University of Ireland, Maynooth, Co. Kildare.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Jan) 28 (1) 153-63. Journal code: EN5. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199805
ENTRY WEEK: 19980503

AB We have used a murine respiratory challenge model to examine the local T cell responses in the lung during infection with Bordetella pertussis. T cells from lung parenchyma and airways of naive and infected mice were refractory to both antigen and mitogen stimulation in the presence of lung macrophages. Furthermore irradiated mononuclear cells from the lungs suppressed antigen and mitogen-induced proliferation, but not IFN-gamma production, by splenic T cells. Removal of macrophages and stimulation of purified lung T cells in the presence of irradiated splenic antigen-presenting cells fully restored the response to mitogen. However, T cells purified from the lung during the acute phase of infection with B. pertussis failed to proliferate or produce detectable levels of IL-2, IL-4, IL-5 or IFN-gamma in response to purified bacterial antigens. In contrast, splenic T cells from these animals produced high levels of IL-2 and IFN-gamma and proliferated strongly to a range of bacterial components. Phenotypic analysis of bronchoalveolar lavage cells during the course of infection revealed transient infiltration of neutrophils, followed by macrophages, CD4+ T cells and smaller numbers of CD8+ T cells and gammadelta+ T cells. Cell surface expression of B7 on infiltrating macrophages and **CTLA-4** on T cells did not change significantly during infection. However, expression of the CD28 co-stimulatory molecule was profoundly reduced on lung T cells during the acute phase of infection. In contrast, lung T cells from mice primed by B. pertussis infection or vaccination were resistant to CD28 down-regulation. These results suggest compartmentalization of T cell responses between the lung and the periphery during B. pertussis infection and that B. pertussis may have immunomodulatory properties on local T cell populations in the lungs of naive mice.

L89 ANSWER 16 OF 37 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-402620 [37] WPIDS
DOC. NO. NON-CPI: N1997-334817
DOC. NO. CPI: C1997-129957
TITLE: New **CTLA4**-modified immunoglobulin fusion proteins - used for e.g. treating auto immune diseases and allergies, or for inhibiting transplantation rejection.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): CARSON, J; GRAY, G S; JAVAHERIAN, K; JELLIS, C L; RENNERT, P D; SILVER, S
PATENT ASSIGNEE(S): (REPK) REPLIGEN CORP
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 9728267 A1 19970807 (199737)* EN 104
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9722554 A 19970822 (199801)
EP 877812 A1 19981118 (199850) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9728267	A1	WO 1997-US1698	19970203
AU 9722554	A	AU 1997-22554	19970203
		WO 1997-US1698	19970203
EP 877812	A1	EP 1997-905730	19970203
		WO 1997-US1698	19970203

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9722554	A	Based on	WO 9728267
EP 877812	A1	Based on	WO 9728267

PRIORITY APPLN. INFO: US 1996-595590 19960202
AB WO 9728267 A UPAB: 19970915
A novel isolated nucleic acid encodes a **CTLA4**-immunoglobulin (Ig) fusion protein, and comprises a nucleotide sequence encoding a first peptide having **CTLA4** activity, and a nucleotide sequence encoding a second peptide comprising an Ig constant region which is modified to reduce at least one constant region-mediated biological effector function.

USE - The **CTLA4**-Ig fusion proteins can be used for inhibiting the interaction of a **CTLA4** ligand on an antigen presenting cell (APC) with a receptor for the **CTLA4** ligand on a T cell (claimed). They can also be used for general immunosuppression and to induce antigen-specific T cell tolerance. They can be used for treating autoimmune diseases such as diabetes mellitus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, and autoimmune thyroiditis (claimed). They can also be used for treating allergy, for inhibiting graft-versus host disease in a bone marrow transplant recipient, or for inhibiting rejection of transplanted cells in a transplant recipient (claimed). They can also be used for immunomodulation, to produce anti-**CTLA4** antibodies, to purify **CTLA4** ligands and in screening assays. The **CTLA4** extracellular domain products have similar uses to the **CTLA4**-Ig fusion proteins.

ADVANTAGE - Use of the modified fusion proteins provides reduced Ig constant region-mediated biological effector mechanisms, such as **complement**-mediated cell lysis, Fc receptor-mediated phagocytosis or antibody-dependent cellular cytotoxicity, all of which may induce detrimental side effects.

Dwg.0/8

L89 ANSWER 17 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 4
ACCESSION NUMBER: 1997:274516 BIOSIS
DOCUMENT NUMBER: PREV199799566234
TITLE: Costimulation through B7-2 (CD86) is required for the induction of a lung mucosal helper cell 2 (TH2) immune response and altered airway responsiveness.
AUTHOR(S): Tsuyuki, Shogo; Tsuyuki, Junko; Einsle, Karin; Kopf,

Manfred; Coyle, Anthony J. (1)
CORPORATE SOURCE: (1) Dep. Experimental Therapeutics, Millennium Pharm., Cambridge, MA 02139-4815 USA
SOURCE: Journal of Experimental Medicine, (1997) Vol. 185, No. 9, pp. 1671-1679.
ISSN: 0022-1007.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The recruitment of eosinophils into the airways after allergen exposure is dependent on interleukin (IL) 5 secreted from antigen-specific CD4+ T cells of the T helper cell (Th) 2 subset. However, while it is established that costimulation through CD28 is required for TCR-mediated activation and IL-2 production, the importance of this mechanism for the induction of a Th2 immune response is less clear. In the present study, we administered the fusion protein **CTLA-4** immunoglobulin (1g) into the lungs before allergen provocation to determine whether CD28/**CTLA-4** ligands are required for allergen-induced eosinophil accumulation and the production of Th2 cytokines. Administration of **CTLA-4** Ig inhibited the recruitment of eosinophils into the lungs by 75% and suppressed IgE in the bronchoalveolar lavage fluid. **CTLA-4** Ig also inhibited the production of IL-4, IL-5, and IL-10 by 70-80% and **enhanced interferon-gamma** production from CD3-T cell receptor-activated lung Thy1.2+ cells. Allergen exposure upregulated expression of B7-2, but not B7-1, on B cells from the lung within 24 h. Moreover, airway administration of an anti-B7-2 monoclonal antibody (mAb) inhibited eosinophil infiltration, IgE production, and Th2 cytokine secretion comparable in magnitude to that observed with **CTLA-4** Ig. Treatment with an anti-B7-1 mAb had a small, but significant effect on eosinophil accumulation, although was less effective in inhibiting Th2 cytokine production. The anti-B7-2, but not anti-B7-1, mAb also inhibited antigen-induced airway hyperresponsiveness in vivo. In all of the parameters assessed, the combination of both the anti-B7-1 and anti-B7-2 mAb was no more effective than anti-B7-2 mAb treatment alone. We propose that strategies aimed at inhibition of CD28 interactions with B7-2 molecules may represent a novel therapeutic target for the treatment of lung mucosal allergic inflammation.

L89 ANSWER 18 OF 37 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:597333 CAPLUS
DOCUMENT NUMBER: 127:277067
TITLE: The role of the B7 costimulatory pathway in experimental cold ischemia/reperfusion injury
AUTHOR(S): Takada, Moriatsu; Chandraker, Anil; Nadeau, Karl C.; Sayegh, Mohamed H.; Tilney, Nicholas L.
CORPORATE SOURCE: Surgical Research Laboratory and Department of Surgery, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: J. Clin. Invest. (1997), 100(5), 1199-1203
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ischemia/reperfusion injury assocd. with organ retrieval and storage influences the development of chronic graft dysfunction, the major clin. problem in solid organ transplantation. The potential role of mononuclear cells (T cells and monocyte/macrophages) in this type of injury is unknown. Inbred male Lewis rats were uninephrectomized and the left kidney perfused in situ with 10 mL of iced University of Wisconsin soln. Immunohistol. studies showed mononuclear cell infiltration of the ischemic organs assocd. with the upregulation of MHC class II antigen expression.

Reverse transcriptase-PCR indicated that T cell assocd. cytokines and monocyte/macrophage activation markers/products are upregulated early after the ischemic insult. B7 expression occurred within 24 h and peaked at 3 d. Plasma creatinine levels rose transiently with complete recovery of renal function by 5 d. Animals began to develop progressive proteinuria after 8-12 wk, indicative of the long-term functional consequences of early ischemia/reperfusion injury. Blockade of T cell CD28-B7 costimulation with **CTLA41g** resulted in significant **inhibition** of T cell and **macrophage** infiltration and activation in situ. Treated animals did not exhibit transient renal dysfunction, nor developed proteinuria over time. This is the first demonstration that blocking T cell costimulatory activation in the absence of alloantigen can prevent the early and late consequences of ischemia/reperfusion injury.

L89 ANSWER 19 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1997:345733 BIOSIS
DOCUMENT NUMBER: PREV199799644936
TITLE: The IgV domain of human B7-2 (CD86) is sufficient to co-stimulate T lymphocytes and induce cytokine secretion.
AUTHOR(S): Rennert, Paul (1); Furlong, Kimberly; Jellis, Cindy; Greenfield, Edward; Freeman, Gordon J.; Ueda, Yuji; Levine, Bruce; June, Carl H.; Gray, Gary S.
CORPORATE SOURCE: (1) Biogen Inc., 14 Cambridge Center, Cambridge, MA 02142 USA
SOURCE: International Immunology, (1997) Vol. 9, No. 6, pp. 805-813.
ISSN: 0953-8178.
DOCUMENT TYPE: Article
LANGUAGE: English
AB B7-1 (CD80) and B7-2 (CD86) are genetically and structurally related molecules expressed on antigen-presenting cells. Both bind CD28 to co-stimulate T lymphocytes, resulting in proliferation and cytokine production. The extracellular portions of B7-1 and B7-2 which bind to CD28 and **CTLA-4** are related to Ig variable (V) and Ig constant (C) domain sequences. Recent reports have described splice variant forms of B7 proteins which occur in vivo and are of unknown function. Here we describe soluble recombinant forms of B7-1 and B7-2 containing either both of the Ig-like extracellular domains or the individual IgV or IgC domains coupled to an Ig Fc tail. Soluble B7-1 and B7-2 bind to CD28 and **CTLA-4**, and effectively co-stimulate T lymphocytes resulting in their proliferation and the secretion of cytokines. Furthermore, the IgV domain of B7-2 binds CD28 and **CTLA-4**, competes with B7-1 and B7-2 for binding to these receptors, and co-stimulates T lymphocytes. Cross-linked soluble B7-2v was the most potent co-stimulatory molecule tested and was active at a concentration ~100-fold lower than cross-linked soluble B7-1 or B7-2 proteins. When bound to tosyl-activated beads, B7-2v was capable of sustaining multiple rounds of T cell expansion. These data **complement** the description of naturally occurring variants to suggest that T cell co-stimulation in vivo may be regulated by soluble or truncated forms of B7 proteins.

L89 ANSWER 20 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1997:204554 BIOSIS
DOCUMENT NUMBER: PREV199799503757
TITLE: Immunomodulatory effects of a plasmid expressing B7-2 on human immunodeficiency virus-1-specific cell-mediated immunity induced by a plasmid encoding the viral antigen.
AUTHOR(S): Tsuji, Takashi; Hamajima, Kenji; Ishii, Norihisa; Aoki, Ichiro; Fukushima, Jun; Xin, Ke-Qin; Kawamoto, Susumu;

Sasaki, Shin; Matsunaga, Kei-Ichiro; Ishigatsubo, Yoshiaki; Tani, Kenji; Okubo, Takao; Okuda, Kenji (1)
CORPORATE SOURCE: (1) Dep. Bacteriology, Yokohama City Univ. Sch. Med., 3-9 Fukuura, Kanazawa-ku, Yokohama 236 Japan
SOURCE: European Journal of Immunology, (1997) Vol. 27, No. 3, pp. 782-787.
ISSN: 0014-2980.
DOCUMENT TYPE: Article
LANGUAGE: English
AB B7 co-stimulation is essential for activating resting T cells following antigen recognition by the T cell receptor. To determine whether B7 has adjuvant activities on human immunodeficiency virus type-1 (HIV-1)-specific immunity induced by inoculation of a plasmid encoding HIV-1 env and rev (DNA vaccine), B7-1 and B7-2 expression plasmids were co-inoculated with the DNA vaccine. The delayed-type hypersensitivity response and cytotoxic T lymphocyte (CTL) activity were significantly enhanced when B7-2 expression plasmid was co-inoculated with the DNA vaccine, but were unaffected when the B7-1 expression plasmid was used with the vaccine instead. The immunological response enhanced by B7-2 decreased below the level of mice immunized with the DNA vaccine in combination with **CTLA4Ig**, an inhibitor of the B7/CD28 co-stimulatory signal, suggesting that this signal is critical for the enhanced response induced by co-inoculation of the DNA vaccine and B7-2 expression plasmid. This **enhancement** appeared to occur via an **interferon-gamma** (IFN-gamma)-dependent mechanism, as combined administration of the B7-2 plasmid and neutralizing anti-IFN-gamma antibody abrogated the virus-specific cell-mediated immunity. These results suggest that this gene-based co-inoculation strategy using HIV-1 viral antigen and B7-2 costimulatory molecule could be a powerful means of combating HIV-1 infection.

L89 ANSWER 21 OF 37 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:708304 CAPLUS
DOCUMENT NUMBER: 125:326411
TITLE: Inhibiting rejection of a graft
INVENTOR(S): Strom, Terry B.
PATENT ASSIGNEE(S): Beth Israel Hospital Association, USA
SOURCE: PCT Int. Appl., 45 pp
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9631229	A1	19961010	WO 1996-US4717	19960405

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1995-417077 19950405
AB Disclosed are methods for inhibiting rejection of a graft in a patient. The methods involve treating the graft with a mol. which binds to a co-stimulatory protein of antigen-presenting cells. The co-stimulatory protein is selected from LFA-3, CD48, CD40, B7, B7-1, B7-2 and B7-3. Useful mols. include chimeras having enzymically inactive polypeptides bonded to polypeptides which bind to co-stimulatory proteins of antigen-presenting cells. Also disclosed, are chimeric mols. composed of lytic IgG, Fc bonded to CD2, CD28, CD40L, or **CTLA-4**. In addn., disclosed are methods for inhibiting rejection of a graft in a patient; the methods involve treating the brain dead, beating heart donor of the graft, prior to removal of the graft from the donor, to render the

graft less susceptible to rejection by the patient.

L89 ANSWER 22 OF 37 MEDLINE
ACCESSION NUMBER: 97057261 MEDLINE
DOCUMENT NUMBER: 97057261
TITLE: Blockade of T-cell costimulation prevents development of experimental chronic renal allograft rejection [see comments].
COMMENT: Comment in: Proc Natl Acad Sci U S A 1996 Oct 29;93(22):12072-5
AUTHOR: Azuma H; Chandraker A; Nadeau K; Hancock W W; Carpenter C B; Tilney N L; Sayegh M H
CORPORATE SOURCE: Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
CONTRACT NUMBER: RO1AI-31100 (NIAID)
R29AI-34965 (NIAID)
RO1DK-46190 (NIDDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Oct 29) 93 (22) 12439-44. Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199702
ENTRY WEEK: 19970204
AB Blocking CD28-B7 T-cell costimulation by systemic administration of **CTLA4Ig**, a fusion protein which binds B7 molecules on the surface of antigen-presenting cells, prevents rejection and induces tolerance in experimental acute allograft rejection models. We tested the effect of **CTLA4Ig** therapy on the process of chronic renal allograft rejection using an established experimental transplantation model. F344 kidneys were transplanted orthotopically into bilaterally nephrectomized LEW recipients. Control animals received low dose cyclosporine for 10 days posttransplantation. Administration of a single injection of **CTLA4Ig** on day 2 posttransplant alone or in addition to the low dose cyclosporine protocol resulted in improvement of long-term graft survival as compared with controls. More importantly, control recipients which received cyclosporine only developed progressive proteinuria by 8-12 weeks, and morphological evidence of chronic rejection by 16-24 weeks, including widespread transplant arteriosclerosis and focal and segmental glomerulosclerosis, while animals treated with **CTLA4Ig** alone or in addition to cyclosporine did not. Competitive reverse transcriptase-PCR and immunohistological analysis of allografts at 8, 16, and 24 weeks showed attenuation of lymphocyte and macrophage infiltration and activation in the **CTLA4Ig**-treated animals, as compared with cyclosporine-alone treated controls. These data confirm that early blockade of the CD28-B7 T-cell costimulatory pathway prevents later development and evolution of chronic renal allograft rejection. Our results indicate that T-cell recognition of alloantigen is a central event in initiating the process of chronic rejection, and that strategies targeted at blocking T-cell costimulation may prove to be a valuable clinical approach to preventing development of the process.

L89 ANSWER 23 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1996:268552 BIOSIS
DOCUMENT NUMBER: PREV199698824681
TITLE: Interactions of CD80 and CD86 with CD28 and **CTLA4**.
AUTHOR(S): Ellis, Jonathan H. (1); Burden, M. Neil; Vinogradov, Dimitri V.; Linge, Claire; Crowe, J. Scott

CORPORATE SOURCE: (1) Immunopathol. Unit, Glaxo-Wellcome Med. Res. Cent., Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY UK
SOURCE: Journal of Immunology, (1996) Vol. 156, No. 8, pp. 2700-2709.
ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English

AB CD80 and CD86 are cell surface glycoproteins expressed on a variety of professional APCs. They have attracted much attention due to their function as potent costimulators of T lymphocyte function through their interaction with CD28 and possibly **CTLA4**. Because inhibitors of this interaction may have therapeutic relevance in human autoimmune disease, we investigated the properties of linear peptides derived from conserved regions of **CTLA4** and CD80 known to be essential for binding. None of these peptides were sufficient to bind ligand, nor did they act as potent competitive inhibitors. Conformationally constrained versions of the **CTLA4** motif were also inactive. These results suggested that other parts of the proteins are important in determining binding, so a series of modified CD80 and CD86 molecules were constructed in an attempt to identify other binding determinants. Insertion of two residues between the two Ig domains of CD80 resulted in decreased affinity for **CTLA4**, but a similar mutation in CD86 was without effect. We also identified another asymmetry between CD80 and CD86 in that the V domain of CD86 but not that of CD80 is sufficient for **CTLA4** binding. The CD86-V domain appears to have **CTLA4** binding properties equivalent to that of intact CD86. These data illustrate a fundamental difference between these costimulatory molecules and suggest a mechanism by which they may be differentially recognized by receptors on the T cell surface.

L89 ANSWER 24 OF 37 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:187793 CAPLUS
DOCUMENT NUMBER: 124:229804
TITLE: Chronic cardiac rejection in the LEW to F344 rat model. Blockade of CD28-B7 costimulation by **CTLA4Ig modulates** T cell and **macrophage** activation and attenuates arteriosclerosis
AUTHOR(S): Russell, Mary E.; Hancock, Wayne W.; Akalin, Enver; Wallace, Africa F.; Glysing-Jensen, Troels; Willett, Theresa A.; Sayegh, Mohamed H.
CORPORATE SOURCE: Harvard School Public Health, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: J. Clin. Invest. (1996), 97(3), 833-8
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **CTLA4Ig**, a fusion protein that blocks CD28-B7 costimulation, was studied in a LEW to F344 rat model of chronic cardiac rejection. In rats treated with a single dose of **CTLA4Ig** (0.5 mg i.p.) d 2 after transplantation, allografts survived significantly longer (>70 d in 64%) than in untreated controls or rats treated with control Ig (all rejected within 25 d). Only 25% of grafts from rats treated with a single, high-dose of cyclosporine A (25 mg/kg, 2 d after transplantation) survived longer than 70 d. Reverse transcriptase PCR and immunostaining analyses of tissue from 75-d, **CTLA4Ig**-treated allografts showed reduced expression of the T cell factor IFN-.gamma. and macrophage activation factors monocyte chemoattractant protein-1, inducible nitric oxide synthase, and galactose/N-acetylgalactosamine macrophage lectin, as well as TGF-.beta.. Grafts from long-term survivors (>120 d) treated with **CTLA4Ig** showed significant redns. in the frequency and severity of

arteriosclerosis in comparison with cyclosporine A-treated rats. Thus, T cell activation is a proximal event in the cascade that culminates in the arteriosclerosis of chronic rejection. Strategies for blocking T cell costimulation may help prevent chronic rejection in clin. transplantation.

L89 ANSWER 25 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1996:479723 BIOSIS
DOCUMENT NUMBER: PREV199699194979
TITLE: CD28: A signalling perspective.
AUTHOR(S): Ward, Stephen G.
CORPORATE SOURCE: Dep. Pharmacol., Sch. Pharm. Pharmacol., Univ. Bath, Bath BA2 7AY UK
SOURCE: Biochemical Journal, (1996) Vol. 318, No. 2, pp. 361-377. ISSN: 0264-6021.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB CD28 and the related molecule cytotoxic T lymphocyte-associated molecule-4 (**CTLA-4**), together with their natural ligands B7.1 and B7.2, have been implicated in the differential regulation of several immune responses. CD28 provides signals during T cell activation which are required for the production of interleukin 2 and other cytokines and chemokines, and it has also been implicated in the regulation of T cell anergy and programmed T cell death. The biochemical signals provided by CD28 are cyclosporin A-resistant and **complement** those provided by the T cell antigen receptor to allow full activation of T cells. Multiple signalling cascades which may be independent of, or dependent on, protein tyrosine kinase activation have been demonstrated to be activated by CD28, including activation of phospholipase C, p21-ras, phosphoinositide 3-kinase, sphingomyelinase/ceramide and 5-lipoxygenase. The relative contributions of these cascades to overall CD28 signalling are still unknown, but probably depend on the state of activation of the T cell and the level of CD28 activation. The importance of these signalling cascades (in particular the phosphoinositide 3-kinase-mediated cascade) to functional indications of CD28 activation, such as interleukin 2 gene regulation, has been investigated using pharmacological and genetic manipulations. These approaches have demonstrated that CD28-activated signalling cascades regulate several transcription factors involved in interleukin 2 transcriptional activation. This review describes in detail the structure and expression of the CD28 and B7 families, the functional outcomes of CD28 ligation and the signalling events that are thought to mediate these functions.

L89 ANSWER 26 OF 37 MEDLINE
ACCESSION NUMBER: 97040551 MEDLINE
DOCUMENT NUMBER: 97040551
TITLE: Triggering of natural killer cells by the costimulatory molecule CD80 (B7-1).
AUTHOR: Chambers B J; Salcedo M; Ljunggren H G
CORPORATE SOURCE: Microbiology and Tumor Biology Center, Karolinska Institute, Stockholm, Sweden.
SOURCE: IMMUNITY, (1996 Oct) 5 (4) 311-7. Journal code: CCF. ISSN: 1074-7613.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY WEEK: 19970204
AB NK cell-mediated cytotoxicity is influenced by triggering as well as inhibitory signals. The identification of inhibitory signals provided by MHC class I molecules has recently attracted significant attention. Much

less is known about putative triggering signals. Using purified populations of mouse NK cells, we demonstrate that the CD80 (B7-1) gene product functions as a triggering signal for NK cell-mediated cytotoxicity. The strength of this response is such that it overrides the protection mediated by MHC class I molecules. Triggering of mouse NK cells by B7-1 occurred even in the absence of CD28 and could not be blocked by either anti-CD28 or anti-**CTLA-4** antibodies. NK cells may thus, at least in part, use receptors other than CD28 and **CTLA-4** in their interaction with B7-1. Furthermore, we demonstrate that bone marrow-derived macrophages and dendritic cells are highly susceptible to lysis by autologous NK cells.

L89 ANSWER 27 OF 37 MEDLINE
ACCESSION NUMBER: 96094451 MEDLINE
DOCUMENT NUMBER: 96094451
TITLE: Suppressor T cell-activating macrophages in ultraviolet-irradiated human skin induce a novel, TGF-beta-dependent form of T cell activation characterized by deficient IL-2r alpha expression.
AUTHOR: Stevens S R; Shibaki A; Meunier L; Cooper K D
CORPORATE SOURCE: Department of Dermatology, University of Michigan Medical School, Ann Arbor 48109, USA.
CONTRACT NUMBER: RO-1 AR-41642-03 (NIAMS)
SOURCE: JOURNAL OF IMMUNOLOGY, (1995 Dec 15) 155 (12) 5601-7. Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199603
AB Because UV-induced epidermal macrophages (UV-Mph) preferentially activate CD4+ T suppressor-inducer cells and induce tolerance, we hypothesized that they differentially up-regulate T cell early activation genes compared with constitutive epidermal APC, Langerhans cells. We used epidermal cells from UV-exposed (UV-EC) and control (C-EC) human skin to stimulate allogeneic CD4+ T lymphocytes. Reverse transcriptase-PCR revealed that both C-EC (Langerhans cells) and UV-EC (UV-Mph) induced 10(3)- to 10(6)-fold increases in IL-2 mRNA. However, while T cells stimulated by C-EC for 48 h showed a greater than 10(3)-fold increase in IL-2R alpha mRNA, those stimulated by UV-EC did not (n = 5, p = 0.004). Flow cytometry demonstrated that 4.1 +/- 2.3% of unstimulated CD4+ lymphocytes expressed cell surface IL-2R alpha, which increased to 15.7 +/- 1.8% upon stimulation by C-EC for 48 h, but stimulation by UV-EC failed to increase the IL-2R alpha+ population (n = 3, p = 0.038). The addition of neutralizing anti-TGF-beta Abs to UV-EC-stimulated cultures restored CD4+ cell surface IL-2R alpha expression to 12.9 +/- 0.2%. CD4+ T cell activation by UV-Mph is distinct from previously described models of tolerance such as Th2 activation (IFN-gamma mRNA was induced and IL-4 mRNA was not) and Th1 anergy (IL-2 mRNA levels induced by UV-EC and C-EC were similar). Furthermore, costimulatory signals were provided by UV-Mph; **CTLA4**-Ig and LFA-3-Ig fusion proteins and Abs to CD2, LFA-3, LFA-1, and ICAM-1 inhibited UV-Mph-induced T cell proliferation. Thus, the altered immune outcome induced by UV-Mph (tolerization) compared with Langerhans cells (sensitization) is reflected as a novel mechanism of initial CD4+ T cell early activation gene expression characterized by TGF-beta-dependent deficient IL-2R alpha expression.

L89 ANSWER 28 OF 37 MEDLINE
ACCESSION NUMBER: 95286865 MEDLINE
DOCUMENT NUMBER: 95286865

TITLE: Cloning and characterization of allograft inflammatory factor-1: a novel macrophage factor identified in rat cardiac allografts with chronic rejection.
AUTHOR: Utans U; Arceci R J; Yamashita Y; Russell M E
CORPORATE SOURCE: Harvard School of Public Health, Boston, Massachusetts 02115, USA.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1995 Jun) 95 (6) 2954-62.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-U17919; GENBANK-U49392
ENTRY MONTH: 199509
AB The development of arteriosclerotic lesions in the Lewis to F344 rat model of chronic cardiac rejection is characterized by macrophage adhesion to the vessel lumen and macrophage infiltration in the neointima prior to smooth muscle cell accumulation. We report the cloning and characterization of allograft inflammatory factor-1 (AIF-1), a novel cDNA that is expressed early and persistently in chronically rejecting cardiac allografts but is absent in cardiac syngrafts and host hearts. The full-length cDNA codes for a hydrophilic polypeptide of 17 kD that contains a 12-amino acid region similar to an EF-hand (calcium-binding) domain. In cardiac allografts AIF-1 transcripts and protein localized to infiltrating mononuclear cells. Analysis of isolated cell populations confirmed that AIF-1 was selectively expressed in macrophages and neutrophils and demonstrated that AIF-1 transcripts could be upregulated by sixfold after stimulation with the T cell-derived cytokine IFN-gamma. Treatment with a diet deficient in essential fatty acids (which attenuates arteriosclerosis) or **CTLA-4** Ig (which blocks lymphocyte activation) significantly decreased AIF-1 transcript levels. Upregulation of AIF-1 in the setting of T cell activation suggests that it may play a role in macrophage activation and function.

L89 ANSWER 29 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1995:409687 BIOSIS
DOCUMENT NUMBER: PREV199598423987
TITLE: Ex vivo coating of islet cell allografts with murine **CTLA4**/Fc promotes graft tolerance.
AUTHOR(S): Steurer, Wolfgang; Nickerson, Peter W.; Steele, Alan W.; Steiger, Jurg; Zheng, Xin Xiao; Strom, Terry B. (1)
CORPORATE SOURCE: (1) Dep. Med., Div. Immunol., Beth Israel Hosp., 330 Brookline Ave., Boston, MA 02215 USA
SOURCE: Journal of Immunology, (1995) Vol. 155, No. 3, pp. 1165-1174.
ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English
AB To test the hypothesis that blockade of B7-triggered costimulation by donor cells could preclude allograft rejection, we coated crude islet allograft preparations in vitro for 1 h with a murine **CTLA4**/Fc fusion protein. Murine **CTLA4**/Fc blocks the proliferative response in primary mixed lymphocyte cultures (MLC) and Con A-stimulated murine spleen cell cultures by 85 to 95%. Responder cells from a primary MLC containing mCTLA4/Fc were hyporesponsive upon restimulation to the same stimulator cells in a secondary MLC lacking mCTLA4/Fc. Because of mutations in the Fc-gamma-RI and C'1q binding sites of the Fc portion of the murine **CTLA4**/Fc fusion protein, the molecule binds to, but does not target, cells for Ab-dependent cellular cytotoxicity or

complement-directed cytolysis. Although systemic immunosuppression was not applied, 42% (10 of 24) of B6AF1 recipients of islet allografts pretreated with **CTLA4**/Fc were permanently engrafted. Further, 50% of hosts bearing functioning islet allografts more than 150 days post-transplant were formally proved to be tolerant to donor tissues. A persistent CD4+ and CD8+ T cell infiltrate surrounding, but not invading, islet grafts in tolerant hosts was discerned. In control experiments, 89% (8 of 9) of islet allografts coated with mIgG3, and 100% (n = 10) pretreated with media alone were rejected. Thus, we conclude that 1) B7-triggered costimulation by donor APCs is an important element of rejection, and 2) blockade of the B7 pathway by in vitro allograft manipulation is able to induce tolerance.

L89 ANSWER 30 OF 37 MEDLINE
ACCESSION NUMBER: 95114379 MEDLINE
DOCUMENT NUMBER: 95114379
TITLE: Dendritic cells are the most efficient in presenting endogenous naturally processed self-epitopes to class II-restricted T cells.
AUTHOR: Guery J C; Adorini L
CORPORATE SOURCE: Roche Milano Richerche, Italy..
SOURCE: JOURNAL OF IMMUNOLOGY, (1995 Jan 15) 154 (2) 536-44. Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199504
AB Dendritic cells (DC) are potent APCs, able to induce efficiently primary T cell-mediated responses to foreign Ags. To assess the efficiency of DC, as compared with other APC types, in the in vivo presentation of self-Ags to CD4+ T cells, we analyzed processing and presentation to class II-restricted T cells of endogenous naturally processed self-epitopes constitutively expressed by mouse APC. Mouse beta 2-microglobulin (m beta 2-m) peptides corresponding to residues 26-39 and 24-36 are constitutively presented, in mice expressing m beta 2-m, by I-Ad and I-Ed molecules respectively, as demonstrated by activation of m beta 2-m-specific T cell hybridomas generated in BALB/c beta 2-m-deficient mice. These dominant, naturally processed self-epitopes of m beta 2-m are presented by APC from a variety of tissues, including the thymus. To analyze the relative efficiency of different APC populations in the presentation of self-beta 2-m, the ability of purified DC, macrophages, and large or small B cells to stimulate m beta 2-m-specific T cell hybridomas was tested. Naturally processed self-m beta 2-m epitopes are constitutively presented to T cells by any class II-positive APC tested, but with highest efficiency by splenic and thymic DC, followed by macrophages, large B cells, and small B cells. This hierarchy of self-beta 2-m presentation does not depend on differential processing capacity of these APC populations, and it correlates with expression of **CTLA-4** ligands and ICAM-1 molecules, rather than with expression of class II molecules.

L89 ANSWER 31 OF 37 MEDLINE
ACCESSION NUMBER: 96036890 MEDLINE
DOCUMENT NUMBER: 96036890
TITLE: Priming of T cells with dendritic, macrophage and B cell lines in vivo requires more than surface expression of MHC II and B7 molecules--possible role of CD44 and integrins.
AUTHOR: Lutz M B; Winzler C; Assmann C; Ricciardi-Castagnoli P
CORPORATE SOURCE: CNR Center of Cytopharmacology, University of Milano, Italy.

SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1995) 378 413-7.
Journal code: 2LU. ISSN: 0065-2598.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603

L89 ANSWER 32 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1995:176498 BIOSIS
DOCUMENT NUMBER: PREV199598190798
TITLE: The Costimulatory Molecule B7 Is Expressed on Human Microglia in Culture and in Multiple Sclerosis Acute Lesions.
AUTHOR(S): De Simone, Roberta; Giampaolo, Adele; Giometto, Bruno; Gallo, Paolo; Levi, Giulio; Peschle, Cesare; Aloisi, Francesca (1)
CORPORATE SOURCE: (1) Neurophysiol. Unit, Lab. Organ Syst. Pathophysiol., Ist. Superiore Sanita, Viale Regina Elena 229, 00161 Rome Italy
SOURCE: Journal of Neuropathology & Experimental Neurology, (1995) Vol. 54, No. 2, pp. 175-187.
ISSN: 0022-3069.
DOCUMENT TYPE: Article
LANGUAGE: English
AB B7 is a costimulatory molecule which is expressed on antigen-presenting cells and which plays a pivotal role in T cell activation and proliferation. To elucidate mechanisms regulating intracerebral immune responses, expression of B7 was examined in cultured microglial cells and in brain tissue from control and multiple sclerosis patients. Using immunocytochemical and polymerase chain reaction techniques, we show that B7 was expressed in cultured microglial cells from the human embryonic brain. Microglia also bound the soluble form of the B7 receptor **CTLA-4** (**CTLA-4**-Ig). B7 gene expression and binding of anti-B7 antibodies and **CTLA-4** -Ig **increased** after treatment with **interferon-gamma**. B7 was not inducible in human astrocytes. Human microglia expressed other costimulatory molecules, such as intercellular adhesion molecule-1, LFA-1 and LFA-3. In sections of multiple sclerosis brains, B7 immunoreactivity was detected on activated microglia and infiltrating macrophages within active lesions. In chronic lesions, only perivascular cells were stained. B7 immunoreactivity was undetectable in sections from Alzheimer's disease or normal brain tissue. These data suggest that B7 may be involved in T cell activation and lesion development in multiple sclerosis and that the regulated expression of B7 on microglia may contribute to the local stimulation of T cell proliferation and effector functions.

L89 ANSWER 33 OF 37 MEDLINE
ACCESSION NUMBER: 94321918 MEDLINE
DOCUMENT NUMBER: 94321918
TITLE: Comparative analysis of B7-1 and B7-2 costimulatory ligands: expression and function.
AUTHOR: Hathcock K S; Laszlo G; Pucillo C; Linsley P; Hodes R J
CORPORATE SOURCE: Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892..
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Aug 1) 180 (2) 631-40.
Journal code: I2V. ISSN: 0022-1007.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199411
AB Antigen-specific T cell activation requires the engagement of the T cell receptor (TCR) with antigen as well as the engagement of appropriate costimulatory molecules. The most extensively characterized pathway of costimulation has been that involving the interaction of CD28 and **CTLA4** on the T cell with B7 (now termed B7-1) on antigen presenting cells. Recently, B7-2 a second costimulatory ligand for **CTLA4**, was described, demonstrating the potential complexity of costimulatory interactions. This report examines and compares the expression and function of B7-1 and B7-2. Overall these results indicate that (a) B7-1 and B7-2 can be expressed by multiple cell types, including B cells, T cells, macrophages, and dendritic cells, all of which are therefore candidate populations for delivering costimulatory signals mediated by these molecules; (b) stimulating B cells with either LPS or anti-IgD-dextran induced expression of both B7-1 and B7-2, and peak expression of both costimulatory molecules occurred after 18-42 h of culture. Expression of B7-2 on these B cell populations was significantly higher than expression of B7-1 at all times assayed after stimulation; (c) blocking of B7-2 costimulatory activity inhibited TCR-dependent T cell proliferation and cytokine production, without affecting early consequences of TCR signaling such as induction of CD69 or interleukin 2 receptor alpha (IL-2R alpha); and (d) expression of B7-1 and of B7-2 can be regulated by a variety of stimuli. Moreover, expression of B7-1 and B7-2 can be independently regulated by the same stimulus, providing an additional complexity in the mechanisms available for regulating costimulation and hence immune response.

L89 ANSWER 34 OF 37 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 94275375 MEDLINE
DOCUMENT NUMBER: 94275375
TITLE: B7 and interleukin 12 cooperate for proliferation and interferon gamma production by mouse T helper clones that are unresponsive to B7 costimulation.
AUTHOR: Murphy E E; Terres G; Macatonia S E; Hsieh C S; Mattson J; Lanier L; Wysocka M; Trinchieri G; Murphy K; O'Garra A
CORPORATE SOURCE: DNAX Research Institute, Palo Alto, California 94304-1104..
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Jul 1) 180 (1) 223-31.
Journal code: I2V. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199409
AB We have previously shown that dendritic cells isolated after overnight culture, which can express B7 and are potent stimulators of naive T cell proliferation, are relatively poor at inducing the proliferation of a panel of murine T helper 1 (Th1) clones. Maximal stimulation of Th1 clones was achieved using unseparated splenic antigen presenting cells (APC). An explanation for these findings is provided in the present study where we show that FcR+ L cells transfected with B7 stimulate minimal proliferation of Th1 clones in response to anti-CD3 antibodies, in contrast to induction of significant proliferation of naive T cells. However, addition of interleukin 12 (IL-12) to cultures of Th1 cells stimulated with anti-CD3 and FcR+ B7 transfectants resulted in a very pronounced increase in proliferation and interferon gamma (IFN-gamma) production. Exogenous IL-12 did not affect the B7-induced proliferation of naive T cells. This showed that whereas costimulatory signals delivered via B7-CD28 interaction are

sufficient to induce significant proliferation of naive T cells activated through occupancy of the T cell receptor, Th1 T cell clones require cooperative costimulation by B7 and IL-12. This costimulation was shown to be specific by inhibition of proliferation and IFN-gamma production using chimeric soluble cytolytic T lymphocyte-associated antigen 4-human IgG1Fc (**CTLA4**-Ig) and anti-IL-12 antibodies. Furthermore, the significant antigen specific proliferation and IFN-gamma production by Th1 clones observed when splenocytes were used as APC was almost completely abrogated using **CTLA4**-Ig and anti-IL-12 antibodies. Thus two costimulatory signals, B7 and IL-12, account for the ability of splenic APC to induce maximal stimulation of Th1 clones. IL-10 downregulates the expression of IL-12 by IFN-gamma-stimulated macrophages and this may account largely for t the ability of IL-10 to inhibit APC function of splenic and macrophage APC for the induction of Th1 cell proliferation and IFN-gamma production. Indeed we show that IL-12 can overcome the inhibitory effect of IL-10 for the APC-dependent induction of proliferation and IFN-gamma production by Th1 clones. These results suggest that proliferation by terminally differentiated Th1 clones, in contrast to naive T cells, requires stimulation via membrane-bound B7 and a cytokine, IL-12. It is possible that these signals may result in the activation of unresponsive T cells during an inflammatory response. IL-10, by its role in regulating such innate inflammatory responses, may thus help to maintain these T cells in an unresponsive state.

L89 ANSWER 35 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1993:137259 BIOSIS
DOCUMENT NUMBER: PREV199395070059
TITLE: Proliferation of human T lymphocytes induced with superantigens is not dependent on costimulation by the CD28 counter-receptor B7.
AUTHOR(S): Damle, Nitin K. (1); Klussman, Kerry; Leytze, Gina; Linsley, Peter S.
CORPORATE SOURCE: (1) Bristol-Myers Squibb Pharmaceutical Research Inst., 3005 First Ave., Seattle, WA 98121
SOURCE: Journal of Immunology, (1993) Vol. 150, No. 3, pp. 726-735. ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Staphylococcal enterotoxins, also known as superantigens (SAg), bind class II MHC molecules on APC and upon direct cell-to-cell contact stimulate proliferation of T cells expressing appropriate V-beta gene products. The T cell surface molecule CD28 binds its costimulatory counter-receptor, B7 expressed on APC, and augments IL-2 production and T cell growth. Although the role of B7 costimulation during Ag-specific responses of T cells is established, its involvement during the activation of T cells with SAg has not been examined. Using a soluble Ig C-gamma-1 chimera of **CTLA-4**, a second receptor for B7 and a homologue of CD28, this study examines the role of B7 expressed on APC during the induction of proliferation of CD4+ T cells upon stimulation with SAg (SAg/staphylococcal enterotoxins). **CTLA-4Ig**, which has a higher avidity for B7 than CD28, had no effect on the synthesis of IL-2 as well as proliferative responses of CD4+ T cells induced by SAg presented on allogeneic EBV-transformed B cells, and IFN-gamma-activated endothelial cells. In contrast, T cell proliferation induced by alloAg presentation by the same APC was significantly inhibited by **CTLA-4Ig**. mAb directed at the CD11a/CD18 molecule inhibited both SAg-induced and alloAg-induced proliferation of T cells. AlloAg-primed CD4+ T cells, which expressed both class II MHC and intercellular adhesion molecule-1 but not B7, presented SAg to and induced proliferation of both resting and SAg-primed T cells. These responses were inhibited by mAb directed at CD11a/CD18 but not by **CTLA-4** Rg. These

results suggest that SAg-induced responses differ from those induced by alloAg in that they are not obligatorily dependent on the costimulation by B7. In contrast, adhesive interaction between CD11a/CD18 on T cells and its counter-receptor on SAg-presenting cells is necessary and probably sufficient to support SAg-induced proliferation of T cells.

L89 ANSWER 36 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1994:91928 BIOSIS
DOCUMENT NUMBER: PREV199497104928
TITLE: Superantigen driven T-B lymphocyte interactions are **inhibited** by murine **CTLA-4Ig**.
AUTHOR(S): King, Philip D. (1); August, Avery; Tumang, Joseph R.; Lowenthal, Michael R.; Dupont, Bo; Friedman, Steven M.
CORPORATE SOURCE: (1) Sloan Kettering Inst. Cancer Res., New York, NY USA
SOURCE: Tissue Antigens, (1993) Vol. 42, No. 4, pp. 432. Meeting Info.: 5th International Leukocyte Differentiation Antigens Boston, Massachusetts, USA November 3-7, 1993 ISSN: 0001-2815.
DOCUMENT TYPE: Conference
LANGUAGE: English

L89 ANSWER 37 OF 37 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1994:18476 BIOSIS
DOCUMENT NUMBER: PREV199497031476
TITLE: B70 antigen is a second ligand for CTLA-4 and CD28.
AUTHOR(S): Azuma, Miyuki (1); Ito, Daisuke; Yagita, Hideo (1); Okumura, Ko (1); Phillips, Joseph H.; Lanier, Lewis L.; Somoza, Chamorro
CORPORATE SOURCE: (1) Dep. Immunol., Juntendo Univ. Sch. Med., Hongo 2-1-1, Bunkyo-ku, Tokyo 113 Japan
SOURCE: Nature (London), (1993) Vol. 366, No. 6450, pp. 76-79. ISSN: 0028-0836.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The membrane antigen B7/BB1 (refs 1, 2) is expressed on activated B cells, **macrophages** and dendritic cells, and **binds** to a counter-receptor, CD28, expressed on T lymphocytes and thymocytes. Interaction between CD28 and B7 results in potent costimulation of T-cell activation initiated through the CD3/T-cell receptor complex. Discrepancies between results with anti-CD28 and anti-B7 antibodies have suggested the existence of a second ligand for CD28 and CTLA-4 (refs 3, 6-8). We have generated a monoclonal antibody, IT2, that reacts with a 70K glycoprotein (B70). B70 complementary DNA was cloned from a B-lymphoblastoid cell line library and encodes a new protein of the immunoglobulin superfamily with limited homology to B7. B70 is expressed on resting monocytes and dendritic cells and on activated, but not resting, T, NK and B lymphocytes. IT2 substantially **inhibited** the binding of a **CTLA4**-immunoglobulin fusion protein to human B-lymphoblastoid cell lines and, together with anti-B7 antibody, completely blocked **CTLA-4** binding. Further IT2 efficiently **inhibited** primary allogeneic mixed lymphocyte responses. These findings indicate that B70 is a second ligand for CD28 and CTLA-4 and may play an important role for costimulation of T cells in a primary immune response.

FILE 'HOME' ENTERED AT 10:33:32 ON 14 OCT 1999

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SYSTEM:OS  - DIALOG OneSearch
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         (c) format only 2000 Dialog Corporation
*File 155: MEDLINE has been reloaded. Accession numbers have changed.
  File  55:Biosis Previews(R)  1993-2000/Jul W1
         (c) 2000 BIOSIS
  File  34:SciSearch(R) Cited Ref Sci  1990-2000/Jun W3
         (c) 2000 Inst for Sci Info
  File 434:SciSearch(R) Cited Ref Sci  1974-1989/Dec
         (c) 1998 Inst for Sci Info
  File 340:CLAIMS(R)/US Patent  1950-00/Jun 20
         (c) 2000 IFI/CLAIMS(r)

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8/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08668513 94174971
Antigen presenting cell function of class II positive human nasal chondrocytes.
Bujia J; Alsalameh S; Sittinger M; Hammer C; Wilmes E; Burmester G
Department of Otorhinolaryngology, Ludwig-Maximilians-University of Munich, Klinikum Grosshadern, Germany.
Acta oto-laryngologica (SWEDEN) Jan **1994**, 114 (1) p75-9, ISSN 0001-6489 Journal Code: 1HA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
It is postulated that class II positive chondrocytes may be actively involved in the destruction or **rejection** of vital **transplanted** cartilage **grafts** . To investigate whether human nasal chondrocytes may also function as accessory cells in ongoing immune reactions with cartilage destruction, mixed leukocyte-chondrocyte cultures and antigen presentation assays were performed. Freshly isolated HLA class II antigen negative chondrocytes obtained from nasal septa were not stimulatory to autologous resting T lymphocytes. HLA class II positive chondrocytes treated with gamma-interferon were able to present antigens to autologous activated T cells derived from an antigen (tetanus) specific T cell line. Upon incubation with activated T cells, initially class II negative changed their phenotype resulting in the expression of class II antigens and enabling them to effectively present antigen. These results suggest an active role of chondrocytes in the **rejection** of cartilage **grafts**.

Jan **1994**,
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; Antigen-Presenting Cells--Drug Effects--DE; Cartilage--Cytology--CY; Cartilage--Drug Effects--DE; **Cells**, Cultured; Chloroquine --Pharmacology--PD; Interferon **Type** II--Immunology--IM; Lymphocyte Transformation--Immunology--IM; Nasal Septum--Cytology--CY; Nasal Septum --Drug Effects...

8/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

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Diagnostic and predictive value of an immunohistochemical profile in asymptomatic acute **rejection** of renal allografts.
Copin MC; Noel C; Hazzan M; Janin A; Pruvot FR; Dessaint JP; Lelievre G; Gosselin B
Department of Pathology, Hopital Calmette, Centre Hospitalier et Universitaire de Lille, France.
Transplant immunology (ENGLAND) Sep **1995**, 3 (3) p229-39, ISSN 0966-3274 Journal Code: B32
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Document type: JOURNAL ARTICLE
We have retrospectively studied the diagnostic and predictive value of immunohistochemical characterization of adhesion molecules (ICAM-1, CD54,

VCAM-1) and HLA-DR antigen in a homogeneous clinical group of 36 patients. Between 1 January 1991 and 31 January 1993, 130 patients received a kidney **transplant** in our unit. Biopsies of renal allografts were only performed in asymptomatic patients who had **graft** dysfunction, revealed by an isolated serum creatinine increase. Available frozen samples were included in this study (n = 44). The 35 cases of acute **rejection** diagnosed by biopsy corresponded to mild acute **rejection** according to the Banff classification criteria. First, we compared the expression of HLA-DR, ICAM-1 and VCAM-1 to morphological data to determine if the immunohistochemical data improved the histopathological diagnosis when the interstitial infiltrate was mild with slight tubulitis. We also studied the phenotype of infiltrating cells with monoclonal antibodies directed against T helper cells, T cytotoxic-suppressor cells, activated T cells and macrophages. Expression on tubular epithelium and density of each **type** of **cell** was graded semiquantitatively. Expression of HLA-DR, ICAM-1 and VCAM-1 was observed on tubular epithelium and endothelium in both acute **rejection** and other causes of **graft** dysfunction, limiting its diagnostic value. Activated T cells expressing CD69-AIM (activation inducer molecule) and/or HLA-DR were frequently observed in acute **rejection** (24/35 (69%) and 25/35 (71%) respectively) but not in other causes of renal dysfunction. We then studied the prognostic usefulness of the immunohistochemical profile in acute **rejection** . Of 27 patients, 12 had a progressively decreased renal function or returned to dialysis within one year after **transplantation** while the other 15 had a stable **graft** function after at least 18 months of follow-up. In the group of bad prognosis (n = 12), corticosteroid-resistant **rejection** episodes were significantly more frequent ($p < 0.01$). In this group, nine patients had an overexpression of HLA-DR on tubular epithelium versus one patient in the group of stable **graft** function (chi 2c = 10.57, $p < 0.002$). Seven patients included in the group of bad prognosis showed tubular overexpression of both ICAM-1 and VCAM-1 versus one patient in the other

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      S9  484559  REVIEW
? ds

Set     Items   Description
S1     679897   TRANSPLANT? OR GRAFT?
S2    5093341   CELL??
S3     216883   S1 AND S2
S4     193351   CELL??(5N)TYPE
S5       7015   S1 AND S4
S6     124567   REJECT?
S7       1000   S5 AND S6
S8        507   S7 AND PY<=1995
S9     484559   REVIEW
? s s8 and s9

            507  S8
         484559  S9
     S10       9  S8 AND S9
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
     S11       8  RD (unique items)
? t s11/3,k,ab/1-8


 11/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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